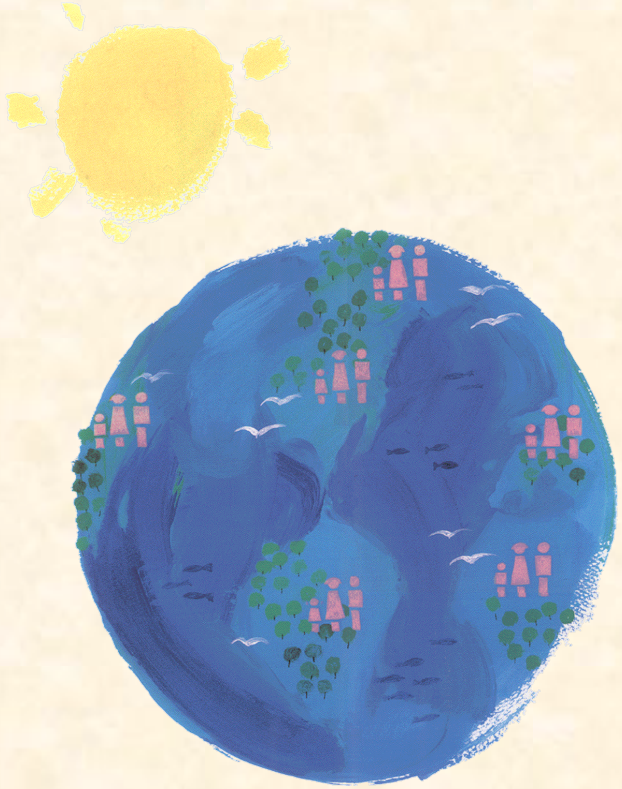
NICEATM

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



ICCVAM Test Method Evaluation Process and Charge to the Expert Panel

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ICCVAM Ocular Expert Panel Meeting
National Institutes of Health
Bethesda, MD
January 11-12, 2005

National Toxicology Program

NIEHS

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA •

The 15 ICCVAM Member Agencies

Regulatory/Research

Consumer Product Safety Commission

Department of Agriculture

Department of the Interior

Department of Transportation

Environmental Protection Agency

Food and Drug Administration

Occupational Safety and Health Administration

Non-Regulatory/Research

Agency for Toxic Substances and Disease Registry

Department of Defense

Department of Energy

National Cancer Institute

National Institute of Environmental Health Sciences

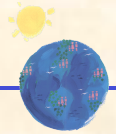
National Institute for Occupational Safety and Health

National Library of Medicine

National Institutes of Health, OD

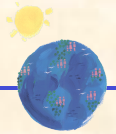
Preamble
ICCVAM Authorization Act (P.L. 106-545)

"To establish, where feasible,
guidelines, recommendations, and regulations
that promote the regulatory acceptance
of new or revised scientifically valid toxicological
tests that protect human and animal health and the
environment
while reducing, refining, or replacing animal tests
and ensuring human safety and product
effectiveness."



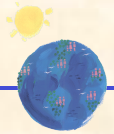
ICCVAM Duties (P.L. 106-545)

- Facilitate and provide guidance on test method development, validation criteria, and validation processes
- Consider petitions from the public for review and evaluation of validated test methods
- Facilitate acceptance of scientifically valid test methods
- Review and evaluate new or revised or alternative test methods applicable to regulatory testing
- Submit test recommendations to Federal agencies
- Facilitate interagency and international harmonization of test methods



NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

- Located at NIEHS
- Functions:
  - Administer ICCVAM
  - Provide scientific and operational support for ICCVAM activities
  - Organize test method peer reviews,expert panel meetings, and workshops
  - Communicate and partner with stakeholders
  - Conduct independent validation studies
- http://iccvam.niehs.nih.gov



What is Validation?

- *The process by which the reliability and relevance of a procedure are established for a specific purpose.*[1]
  - *Reliability:* A measure of the extent to which a test method can be performed reproducibly within and among laboratories over time. It is assessed by determining intra- and inter-laboratory reproducibility and intra-laboratory repeatability.
  - *Relevance:* The extent to which a test method correctly predicts or measures the biological effect of interest. Relevance incorporates consideration of the 'accuracy' of a test method.
- Validation characterizes the usefulness and limitations of a test method for a specific purpose.
- *Adequate validation is a prerequisite for regulatory acceptance consideration*

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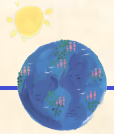
1 *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods;* NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf



Criteria for Test Method Validation[1]

1. Clear statement of proposed use and regulatory rationale
2. Biological basis/mechanistic relationship to effect of interest
3. Formal detailed protocol
4. Reliability adequately assessed
5. Relevance adequately assessed
6. Limitations described
7. All data (raw) available for review
8. Data quality: *Ideally GLPs*
9. Independent scientific peer review

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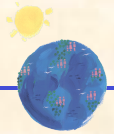
[1] Adapted from: *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods*; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf



Criteria for Test Method Acceptance[1]

1. Fits into the regulatory testing structure
2. Adequately predicts the toxic endpoint of interest
3. Generates data useful for risk assessment
4. Adequate data available for specified uses
5. Robust and transferable
6. Time and cost-effective
7. Adequate animal welfare consideration (3Rs)

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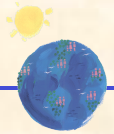
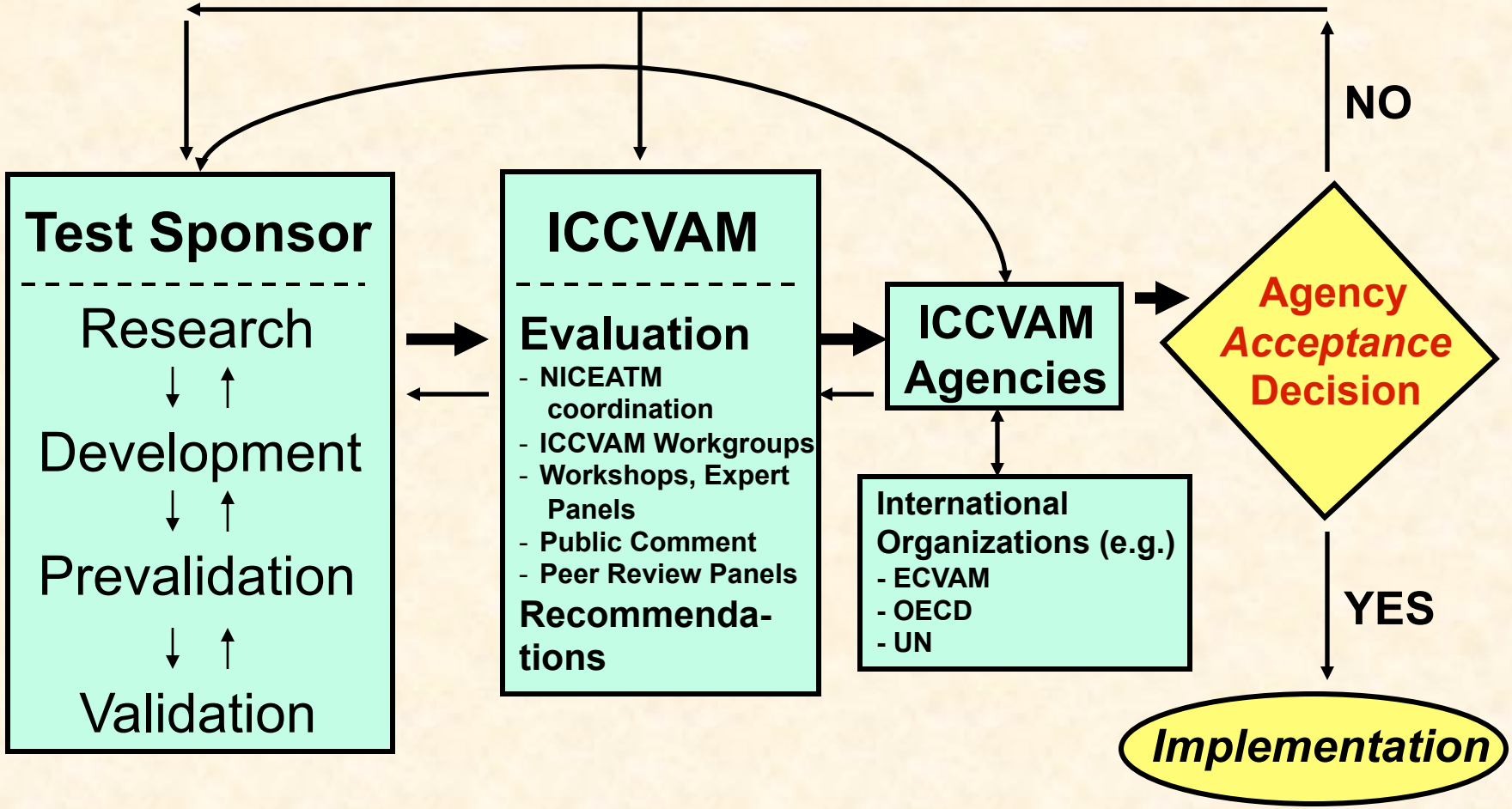
1 Adopted from: *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods*; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf



ICCVAM Test Method Evaluation Process



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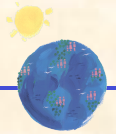
Why ocular hazard/safety testing?

- Several eyelash dyes in the 1930s in the U.S. resulted in permanent eye damage and vision loss
  - The U.S. Food and Drug Act amended to include safety testing of cosmetics in 1938
  - Other products covered in subsequent U.S. laws
- Accidental eye injury is the leading cause of visual impairment in the U.S.
  - More than 1 million eye injuries annually
    - 10-20% result in temporary or permanent vision loss
- Workplace and household chemicals are a significant cause of these injuries
    - NIOSH reported 39,200 workplace chemical-related eye injuries in 1998

Sources: American Academy of Ophthalmology; NIOSH

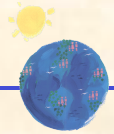
In Vitro Alternatives for Ocular Irritation

- Numerous methods developed in 1980s-90s
- Numerous validation studies conducted in 1990s
- 1993 IRAG workshop
  - Several *in vitro* test methods evaluated as *replacements* for *in vivo* tests
  - No test methods valid as replacements
- However, test guidelines were modified to allow for the use of in vitro test methods following future validation ***and*** acceptance
  - EPA OPPTS,1998
  - GHS: tiered testing strategy, 2003
- EU: will accept positive results for classification as R41 (risk of serious damage to the eye)



In Vitro Ocular Irritation Test Methods

- **European Commission Directive 2004/73/EC (29 April 2004)**
  Regarding: IRE BCOP ICE HET-CAM
  - ***"These tests are not yet validated, and therefore not included in Annex V"***
  - ***Positive results can be used to consider a substance a severe irritant and R41 applied with no further testing***
  - ***"Where a negative result is obtained, an in vivo test should subsequently be required, as the in vitro tests have not been shown to adequately discriminate between eye irritants and non-irritants."***



ICCVAM Ocular Evaluation

Background

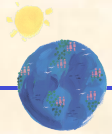
Oct 2003 EPA formal nomination of four ocular evaluation activities

Jan 2004 ICCVAM endorsed all EPA nomination activities as high priority

- Highest priority: evaluation of in vitro screening methods for ocular corrosives/severe irritants
- Ocular Toxicity Working Group established to coordinate evaluation with NICEATM

ICCVAM Ocular Evaluation (cont'd)

March 2004	**Request for Public Comment on the Nominations, and Request for Data on Chemicals Evaluated by *In Vitro* or *In Vivo* Ocular Irritancy Test Methods** – ***Federal Register*** **Notice (69 FR 13859, March 24, 2004)** – **ECVAM distributed Notice to European scientific community**
April 2004	**Request for Nominations of Scientific Experts for Independent Expert Panel** – ***Federal Register*** **Notice (69 FR 21565, April 21, 2004)**
Apr-Oct 2004	**Preparation of 4 Draft Background Review Documents**
Nov 2004	**Notice of an Expert Panel Meeting and the Availability of the Draft BRDs; Request for Comments** – ***Federal Register*** **Notice (69 FR 64081, Nov 3, 2004)**
Dec 2004	**Notice of Additional Data and Analyses** – ***Federal Register*** **Notice (69 FR 70268, Dec 3, 2004)**
Jan 2005	**ICCVAM Expert Panel Meeting**



Charge to the Expert Panel

1. Evaluate, for each of the four test methods, the extent and adequacy that each of the applicable ICCVAM validation and acceptance criteria:

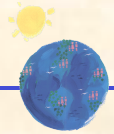
   - Have been addressed, based on available information and data, or
   - Will be addressed in proposed studies

   for the purpose of identifying ocular corrosives and severe irritants in a tiered testing strategy.

Charge to the Expert Panel

2. Develop conclusions and recommendations on:

- Current usefulness and limitations of each of the four test methods for identifying ocular corrosives and severe/irreversible irritants
- The test method protocol that should be used for future testing and validation studies
- Adequacy of proposed optimization and/or validation studies
- Adequacy of reference substances proposed for future validation studies



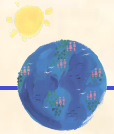
Future ICCVAM Ocular Activities

May 10-11, 2005 — Scientific Symposium on Mechanisms of Chemically-Induced Ocular Injury and Recovery

May 12, 2005 — Scientific Symposium on Minimizing Pain and Distress in Ocular Toxicity Testing

Fall, 2005 — ICCVAM Peer Review Panel Meeting

- Non-animal approaches for evaluating skin and eye irritation potential for antimicrobial cleaning product formulations



ICCVAM Ocular Expert Panel

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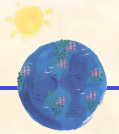

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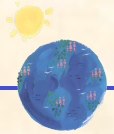
Acknowledgements

Invited Test Method Experts

1. ICE - Dr. Menk Prinsen, TNO-CIVO Institutes, NL
2. HET-CAM - Dr. Klaus Krauser, Abbott Laboratories
3. IRE - Dr. Robert Guest, SafePharm Laboratories Ltd., UK
4. BCOP - Dr. John Harbell, Institute for In Vitro Sciences, Inc.

Organizations Contributing Data

Cosmetics, Toiletries, and Fragrances Assn.(CTFA)
European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)
U.S. Environmental Protection Agency
U.S. Food and Drug Administration
GlaxoSmithKline
ExxonMobil
National Institutes of Health Sciences - Japan
S.C. Johnson
Proctor & Gamble



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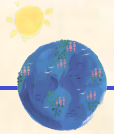
NLM	Vera Hudson
	Jeanne Goshorn
OSHA	Surrender Ahir

* As of December 2004



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